REMARKS/ARGUMENTS

The Pending Claims

Claims 1-15, 17-32, and 38-44 are currently pending. Claims 1-15 are directed to a method of producing a lyophilized tobramycin formulation. Claims 17-28 are directed to a lyophilized tobramycin pharmaceutical formulation. Claims 29-32 are directed to a solution prepared using lyophilized tobramycin. Claims 38-40 are directed to a pharmaceutical dosage form containing lyophilized tobramycin. Claims 41-44 are directed to a method of treating disease involving lyophilized tobramycin.

Discussion of the Claim Amendments

The claim immediately following claim 14 has been amended to change the claim number to 15. As a result, the claims are now consecutively numbered in accordance with 37 U.S.C. § 1.126. Accordingly, the claim objections are moot and should be withdrawn.

Claim 1 has been amended to recite that the liquid composition comprises a solvent comprising about 4.5% by volume or less of tert-butyl alcohol. Support for this amendment can be found in the present specification at paragraph [0026]. Claim 1 has been further amended to recite that the lyophilized tobramycin is in the form of a free-flowing powder. Support for this amendment can be found in the present specification at paragraph [0016].

Claim 20 has been amended to reflect the amendments to claim 1.

Claims 16 and 33-37 have been canceled without prejudice or disclaimer.

Summary of the Office Action

The Office Action objects to the numbering of the claims as not being consecutively numbered. Claim 44 stands rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

Claims 17, 20, 29, 33, and 35 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Nail et al., *J. Pharmaceutical Sciences*, *91*, 1147-1155 (2002) (hereinafter "the Nail publication"). Claims 1-16, 18-19, 21-28, 30-32, 34, and 36-39 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the Nail publication.

Claims 41-44 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent 4,166,144 (Igarashi) (hereinafter "the Igarashi '144 patent") in combination with Lagace et al., *J. Liposome Research, 9(3)*, 301-312 (1999) (hereinafter "the Lagace publication").

Discussion of the Claim Objections

The Office Action objects to the claims for failure to consecutively number the claims. In particular, in the claims as originally filed, the claim immediately following claim 14 was erroneously labeled claim 16. The claim immediately following claim 14 has been relabeled as claim 15. Accordingly, the claim objections should be withdrawn.

Discussion of the Indefiniteness Rejection

The Office Action rejects claim 44 as allegedly indefinite for its recitation of complicated urinary tract infections, and asserts that the metes and bounds of the term "complicated" are not clear. The term "complicated urinary tract infection" is an art-accepted term referring to one of two classifications of urinary tract infections. For example, the U.S. Food and Drug Administration ("FDA") published a "Guidance for Industry" document (hereinafter "the Guidance document") (provided herewith) which can be found on the FDA's web site. The Guidance document refers to two broad categories of labeling for anti-infective drugs in the treatment of urinary tract infections ("UTI"): (1) uncomplicated UTI and (2) complicated UTI and pyelonephritis (the Guidance document at page 2). The Guidance Document further references a guidance document issued by the Infectious Disease Society of America including the categories of uncomplicated UTI and complicated UTI (the Guidance document at page 2). Since the term "complicated urinary tract infections" refers to a recognized classification of urinary tract infections, the term "complicated" is not indefinite. The indefiniteness rejection of claim 44 is improper and should be withdrawn.

Discussion of the Anticipation Rejection

Claims 17, 20, 29, 33, and 35 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by the Nail publication. As noted above, claims 33 and 35 have been canceled. The Nail publication teaches a tobramycin sulfate formulation prepared by subjecting aqueous solutions of tobramycin sulfate to drying, wherein the aqueous solutions of

tobramycin sulfate initially comprise from 5% to 11% t-butanol. Nail publication at Figures 3-6. Pending claims 17, 20, and 29 require that the formulation comprising lyophilized tobramycin is prepared by drying an aqueous solution comprising tobramycin, wherein the aqueous solution of tobramycin initially comprises about 4.5% by volume or less of t-butanol. Thus, the Nail publication fails to teach each and every limitation recited in the pending claims. Accordingly, the anticipation rejection of claims 17, 20, and 29 is improper and should be withdrawn.

Discussion of the Obviousness Rejection of Claims 1-16, 18-19, 21-28, 30-32, 34, and 36-39

Claims 1-16, 18-19, 21-28, 30-32, 34, and 36-39 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the Nail publication. Applicants respectfully traverse the obviousness rejection.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not in applicant's disclosure. See *In re Vaeck*, 947 F2d. 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). For the reasons set forth below, the Office Action has failed to set forth a *prima facie* case of obviousness of claims 1-16.

Pending claims 1-16, 18-19, 21-28, 30-32, and 38-39 require that the initial t-butanol (tert-butyl alcohol) concentration be about 4.5% by volume or less in order to produce lyophilized tobramycin that is a free-flowing powder. In contrast, the Nail publication teaches the use of liquid compositions having an initial t-butanol concentration of not less than at least 5% by volume.

A primary goal of the Nail publication is to minimize the level of residual t-butanol in the lyophilized tobramycin sulfate. Nail publication at 1147 (abstract). The Nail publication sets forth the results of experiments wherein the amount of residual t-butanol after lyophilization was determined as a function of the initial concentration of t-butanol in the

solution. In a first experiment, the residual t-butanol in the product of lyophilization of an 11% tobramycin sulfate solution in water with initial t-butanol concentrations of 5% to 9% was determined. *Id.* at 1152 (Figure 4). Figure 4 of the Nail publication shows that an 11% tobramycin sulfate solution having a 5% initial concentration of t-butanol provides a lyophilized product having a slightly higher residual amount of t-butanol than an 11% tobramycin sulfate solution having a 6% initial concentration of t-butanol. In a second experiment, the residual t-butanol in the product of lyophilization of an 11% tobramycin sulfate solution in water with initial t-butanol concentrations of 5% to 9% and under two different drying conditions was determined. *Id.* (Figure 5). Under both sets of drying conditions, a tobramycin sulfate solution having a 5% initial concentration of t-butanol provides a lyophilized product having a higher residual amount of t-butanol than a tobramycin sulfate solution having a 6% initial concentration of t-butanol (about 0.9% residual t-butanol versus about 0.75% t-butanol after 10 h of drying at 25° C).

The Nail publication fails to teach or suggest a method of producing a pharmaceutical formulation comprising lyophilized tobramycin, wherein the method comprises preparing a liquid composition comprising tobramycin and a solvent comprising about 4.5% by volume or less of t-butanol, and wherein the lyophilized tobramycin is in the form of a free-flowing powder. The experimental results reflected in Figures 4 and 5 indicate that **the residual t-butanol content increases, not decreases, when the initial concentration of t-butanol is less than 5%**. The ordinarily skilled artisan would thus be motivated by the Nail publication to select an amount of t-butanol of about 6% or more, and certainly no less than about 5%, as the Nail publication clearly shows that the use of 5% t-butanol in the lyophilization of tobramycin results in higher levels of residual t-butanol than the use of 6% t-butanol.

In sum, there is no teaching or motivation based on the Nail publication to produce lyophilized tobramycin by the method recited in the pending claims. Accordingly, applicants respectfully request that the obviousness rejection of claims 1-16, 18-19, 21-28, 30-32, and 38-39 be withdrawn.

Discussion of the Obviousness Rejection of Claims 41-44

Claims 41-44 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the Igarashi '144 patent in combination with the Lagace publication. The Office Action

relies on the Igarashi '144 patent for its teaching of a method of treating bacterial infections in humans and animals including, *inter alia*, soft tissue infections and urinary tract infections. The Office Action acknowledges that the Igarashi '144 patent does not teach a treatment method comprising use of lyophilized tobramycin, but relies on the Lagace publication for its disclosure of the efficacy of lyophilized tobramycin against bacteria including, e.g., P. aeruginosa, S. maltophilia, B. cepacia, E. coli, and S. aureus. Applicants traverse the rejection.

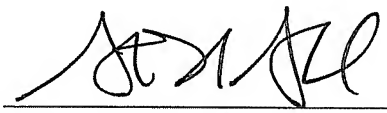
Contrary to the Office Action's assertions, the combination of the Igarashi '144 patent and the Lagace publication does not teach or suggest a method of treating a disease in a patient, which method comprises the use of a formulation comprising lyophilized tobramycin, wherein the lyophilized tobramycin is in the form of a free-flowing powder, let alone lyophilized tobramycin prepared by the method recited in the pending claims. The Lagace publication teaches the use of tobramycin that has been lyophilized at 4° C in *in vitro* antibacterial experiments against several strains of bacteria. Lagace publication at p. 304. Moreover, nothing within the Lagace publication teaches or suggests that the lyophilized tobramycin is in the form a free-flowing powder.

In order to establish a *prima facie* case of obviousness, the reference (or references when combined) must teach all of the claim limitations. In the present case, the combination of the Igarashi '144 patent and the Lagace publication fails to teach all of the claim limitations recited in pending claims 41-44. Accordingly, the obviousness rejection of pending claims 41-44 is improper and should be withdrawn.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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